# I. SYNTHETIC ANALOGS OF TETRAHYDROCANNABINOL

# II. THE AMAROIDS OF AESCHRION EXCELSA

# III. THE CONSTITUENTS OF HELENIUM AUTUMNALE, VAR. CANALICULATA AND H. MICROCEPHALUM

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BENJAMIN FRANKLIN AYCOCK, JR.

B.S., University of North Carolina, 1942
M.S., University of Illinois, 1945

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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## ACKNOWLEDGMENT

The author wishes to express his gratitude to Professor Roger Adams for his guidance and advice during the course of this research.

He is also indebted to Dr. Allen E. Senear for cooperation in the investigations described in Parts II and III of this thesis, and to Mrs. A. R. Johnson and Mr. John Brantley for determination of infrared and ultraviolet absorption spectra.

He takes this opportunity to thank the University of Illinois for the University Fellowship held during the first semester of 1944-1945 and the Allied Chemical and Dye Corporation for a fellowship held for the 1946-1947 school year.

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# PART ONE

# SYNTHETIC ANALOGS OF TETRAHYDRO-CANNABINOL

## Introduction

Chemical investigations of hemp, *Cannabis sativa*, have shown that the intoxicating effect of its preparations is due to a tetrahydrodibenzopyran known as tetrahydrocannabinol (1). While the natural principle has not been synthesized, an isomer differing in the location of a double bond has been prepared and shown to possess typical marihuana activity. In addition, a large number of analogs and homologs have been prepared and tested. Activities are given on the basis of the synthetic isomer as a standard of 1.

The most interesting of these compounds have been 1-hydroxy - 3 - alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro - 6 - dibenzopyrans. Variations in the 3-alkyl group have produced a wide range of activities, the most effective group being 1′-methylalkyl. The preparation of higher homologs in the 1′-methylalkyl series and a study of the effect of distance from the nucleus of a substituent methyl group was the subject for these studies.

## Discussion of Results

New tetrahydrocannabinol homologs were prepared from 3,5-dimethoxybenzamide by conversion to ketones with the appropriate Grignard reagent. From these 5-acylresorcinol dimethyl ethers 5-alkyl resorcinols with branching in the alkyl group were synthesized and used in a Pechmann condensation with ethyl 5-methylcyclohexanone-2-carboxylate. The pyrans obtained upon treatment with methylmagnesium iodide were tested for marihuana activity.

Two new tetrahydrocannabinol homologs with 1′-methyl-

octyl and 1′-methylnonyl groups in the 3- position have been prepared. The peak of activity in the simple 1′-methylalkyl series occurs at the *s*-nonyl homolog, which has an activity of 32, over four times that of the natural compound. The s-decyl derivative has a potency of only 2.08, but the duration of peak effect was five times that of its congeners.

Homologs with three isomeric methylpentyl groups have been prepared, the methyl group being situated at the 2′-, 3′-, and 4′- positions. Activity decreased as the methyl group became increasingly distant from the ring, but all three isomers were more potent than the standard.

Attempts to prepare an analog having an olefinic side chain in the 3- position were unsuccessful, as were attempted syntheses of more soluble homologs.

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# PART TWO

# THE AMAROIDS OF *AESCHRION EXCELSA*

## Introduction

Extracts of the wood of two simarubas, *Quassia amara* and *Aeschrion excelsa,* have long been used as medicinal bitters. Although the bitter principle in "quassia" has been investigated sporadically, very little is known of the chemistry of this material. Clark (1) isolated from *Quassia amara* two isomers which he called quassin and neoquassin, and from *Aeschrion excelsa* he obtained a third isomer, picrasmin.

Each of these three isomers was found to contain two methoxyl groups, and treatement of any of them with dichromate in acetic acid solution led to the formation of a

fourth isomer, isoquassin. Other derivatives of the compounds were prepared, but none gave any insight into the structure of the molecule. The purpose of this research was to isolate and purify the amaroid of *Aeschrion excelsa*, and to study the physical and chemical properties of the compound and its derivatives.

## Discussion of Results

*Aeschrion excelsa* was extracted with water according to Clark's procedure to give a poor yield, 0.06%, of crude amaroid. This material was obviously a mixture, and its components were very difficult to separate. Fractional recrystallization gave a small amount of material which corresponded to a sample of Clark's neoquassin. This neoquassin could also be obtained in 37% yield by subjecting the crude bitter principle to hydrogenation conditions. The proof of identity of these compounds was obtained by infrared absorption spectra.

Isoquassin was prepared from the extract in 70% yield by treatment with dichromate, and its absorption spectrum was very similar to that of Clark's picrasmin. Inasmuch as this is the only pure compound obtained in good yield from the crude material, it appears that elucidation of the structure of the amaroids must start from isoquassin. The presence of a carbonyl group in the wood extract was established by the preparation of a 2,4-dinitrophenylhydrazone. Other elements of the structure were considered on the basis of the infrared absorption spectra.

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# PART THREE

# THE CONSTITUENTS OF *HELENIUM AUTUMNALE*, VAR. *CANALICULATA* AND *H. MICROCEPHALUM*

## Introduction

The genus *Helenium* is quite common in the United States. Many species are toxic to livestock, and some can cause milk to be bitter when they are ingested by cattle. The dried plants are sternutators when dry.

The presence of two compounds has been demonstrated for several members of the genus; helenalin occurring in some, and tenulin in the others. Very little is known concerning the structure of these compounds, although isolation procedures have been perfected and some derivatives have been characterized (1).

To establish a basis for chemical degradation of the helenalin and tenulin molecules by investigation of their gross structure was the purpose of this research.

## Discussion of Results

Extraction of *H. autumnale*, var. *canaliculata* and *H. microcephalum* has been shown to yield tenulin and helenalin, respectively. The presence of two carbon-carbon double bonds and a hydroxyl group in helenalin has been verified by the preparation of tetrahydrohelenalin and acetylhelenalin. Absorption spectra studies of these compounds indicate the presence of a lactone and a carbonyl group.

Dihydrotenulin was prepared from tenulin, and two series of carbonyl derivatives have been obtained from these two compounds. Infrared absorption spectra of these substances are discussed, and the presence of a previously discovered acetyl group as an ester of a vinyl alcohol is postulated. A system which can exhibit some aromatic character is indicated by the ultraviolet absorption spectrum, but the presence

of an ordinary aromatic ring is doubtful.

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## VITA

The author was born in Washington, D. C., on May 18, 1922. After graduation from the public schools of Fremont, North Carolina, in 1938, he entered the University of North Carolina, where he received the degree of Bachelor of Science in Chemistry in June, 1942. In the fall of that year he entered the Graduate School of the University of Illinois as a teaching assistant. He held this position through the summer of 1943, and became a University Fellow in September. In February, 1944, he accepted a full-time teaching assistantship for the second semester. He received the Master of Science degree from the University of Illinois in 1945.

After withdrawal from the University of Illinois in May, 1944, he became a Special Research Assistant in the Chemistry Department of Indiana University on a project of the National Defense Research Committee. Upon the termination of this contract in February, 1945, he transferred to the Explosives Research Laboratory at Bruceton, Pennsylvania, where he was employed by the National Defense Research Committee through a contract with the Carnegie Institute of Technology.

In October of 1945, he resigned from this position to reenter the Graduate School of the University of Illinois as a teaching assistant. He held this position until September, 1946, when he became an Allied Chemical and Dye Fellow for two semesters.